With Dr. Fraser's compts.

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Strophanthus hispidus—*continued:* Pharmacological Action. By Dr Thomas R. Fraser.

(*Abstract.*)

(Read June 3, 1889.)

Strophanthus extract and Strophanthin are substances of great pharmacological activity, as, by subcutaneous administration, Strophanthin produces death in average-sized frogs with a dose of $\frac{1}{4000}$th of a grain, and in rabbits weighing about 3 lbs. with a dose of $\frac{1}{100}$th of a grain. The kind of action is the same with both substances, and therefore Strophanthin may properly be regarded as the active principle of *Strophanthus hispidus*. In my preliminary communications I have already described the more important characteristics of the action, and, therefore, to-night I shall content myself with drawing attention to a few only of these characteristics.

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I have not obtained evidence of any primary action on the brain, medulla oblongata, spinal cord, nor motor nerves. Sensibility, however, is slightly affected; one of the most conspicuous evidences of which is the insensibility of the cornea following the application of dilute solutions to the eye-ball.

In the preliminary communications I have stated that the chief action is that exerted upon the heart, produced when large toxic doses are given by a powerful action upon the heart-muscle.

This action upon the heart-muscle is one which Strophanthus exerts upon all the other striped muscular fibres of the body. These muscles are affected by twitching movements, their tonicity is increased, and, finally, their contractility is destroyed. They are not then, however, flaccid, soft, and alkaline, but hard and acid in reaction. In fact, the condition of the muscles is one of *rigor mortis*, in which the alkaline reaction of the living muscle has given place to the acid reaction of rigor; and, just as the acid reaction of ordinary *rigor mortis* continues until the muscle becomes flaccid in the process of putrefaction, so the acid and hard condition produced by the pharmacological action of Strophanthus remains until putridity causes the muscle again to become alkaline, soft, and flaccid. This prevention of the initial muscular flaccidity of death and precipitation, as it were, of *rigor mortis*, to which I drew attention so long ago as 1870,* has since been recognised by other observers as events in the pharmacological action of digitalis, and of several members of the digitalis group.

The twitches produced in the muscles of the body have been further examined in detached muscles, immersed in normal saline solution to which Strophanthus had been added, and connected with a lever recording the movements on a revolving cylinder. The movements in the detached muscle are thus seen to be very remarkable. At first a faint twitch occurs in an individual muscular fibre, then simultaneous and independent contractions of different fibres rapidly succeed each other, until by and by a perfect tumult of contractions occurs in rapid succession in different muscular fibres, and the lever attached to the muscle is kept in almost constant motion, its excursions being altogether irregular both in time and in extent. [Tracings were shown.] While the muscle is so affected,

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electric stimulation of its motor nerve fails to cause any effect. After the twitching contractions have ceased, the motor nerve regains its influence; and the contractions of the entire muscle, which are now produced by stimulating the nerve, illustrate the condition of increased tonicity produced by Strophanthus. The muscle curve is altogether different from the normal curve. The muscle contracts actively, but, after having contracted, it relaxes with great tardiness; and it is only after several revolutions of a rapidly revolving cylinder that the curve gradually falls to the abscissa. [Curves were shown.]

When Strophanthus is administered by subcutaneous injection to a frog, one of whose muscles, without otherwise deranging its normal relations, is attached to a lever writing on a revolving cylinder, similar changes in contractility are observed, but they are less in degree. [Curves were shown.]

Owing partly to the circumstance that a larger quantity of any substance introduced into the blood is in any given time conveyed to the heart than to any other individual organ or structure of the body, the action of Strophanthus is exerted with the greatest energy and activity upon the heart. With very minute doses, its contractions are rendered slower and more perfect and complete; and with larger doses, the diastolic dilatation of its chambers is reduced until dilatation disappears altogether, and the heart ceases to beat because its muscle can no longer relax. The condition of the muscle becomes the same as that of the other striped muscles under the influence of large doses. It is hard, non-contractile under stimulation, and acid in reaction,—the condition of true *rigor mortis* having been produced as the ultimate stage in the sequence of events in the pharmacological action of Strophanthus. These changes occur even although all the nerve connections of the heart are severed, or the vagus nerve is paralysed by the previous administration of atropine.

The power of an extremely minute quantity of Strophanthus to produce these effects on the heart was illustrated in a series of experiments, in which an attempt was made to determine the minimum quantity required to paralyse the frog's heart. The heart was attached to an apparatus allowing it to pump from a reservoir a fluid which sustained its nutrition for many hours,

and to this fluid a certain dose of Strophanthus was added. The apparatus further recorded the individual contractions of the heart, so as not only to show the rate of contraction, but also the amplitude of each contraction. With very minute doses, and in the early stages of the action of larger doses, the contractions became slower, and an increased volume of fluid was projected from the heart at each contraction. It was found that when the circulating fluid contained Strophanthin in the proportion of one part in ten millions, the characteristic changes were produced. Even the almost inconceivably minute dose which was brought in contact with the heart when a solution of *one in six millions* was used, produced complete stoppage of the heart, in extreme systolic contraction, in less than half an hour. *One part in fifteen millions*, *one part in eighteen millions*, and even *one part in twenty millions* also produced well-marked effects; but these extreme dilutions did not always arrest the heart's contractions, and, as contrasted with the changes produced by less dilute solutions, the slowing of the heart was due to delay during its diastole more than during its systole.

When the exposed heart is observed *in situ* after the administration of Strophanthin, even when the dose is only a minimum lethal one, the changes that are seen are usually those indicating a great increase in the strength and in the duration of systolic contraction, and the ultimate standstill of the heart is, as before described, brought about by the systolic contraction becoming persistent and passing immediately into *rigor mortis*. This increased duration of contraction, with consequent lessening of the dilatation of the heart and of the capacity of its chambers, is not, however, the action which is likely to be serviceable in weak conditions of the organ or in the existence of disabling lesions.

I accordingly made some experiments in which Strophantin was given in rather less than minimum lethal doses—in some experiments by subcutaneous administration, and in others by direct application of a solution to the heart's surface. When care was taken to prevent any irritant, even the air in motion, from reaching the heart, a minute dose produced slowing and a great increase in the amplitude of dilatation, with strong systolic contractions. In some experiments the diastolic pause was so greatly lengthened that the heart remained motionless for two or three minutes, with its

ventricle very large and full of blood; but yet the interrupting systolic contractions were strong, and they completely and deliberately emptied the ventricle of its large accumulation of blood. It was found, however, to be extremely difficult, by any adjustment of the dose, to produce a standstill of the heart in diastole. The heart either recovered altogether, or, in the course of time, the diastolic pauses became briefer, and the systole predominated until the heart ceased to beat in systolic rigidity.

The experiments demonstrated that with doses below the minimum lethal—that is to say, with such doses as would be employed in the therapeutic administration of Strophanthus—both the diastole and the systole of the heart were rendered more perfect, and that the action, therefore, was greatly to increase the working capacity of the heart.

An endeavour was next made to determine upon what structures Strophanthus acts in order to produce the changes that follow the administration of doses less than lethal. The above experiments were repeated after all the nerve connections of the heart with the central nervous system had been divided, and also after the vagus inhibitory apparatus had been paralysed by atropine; but the action that has been described was produced equally well after these modifications had been made. It could not, therefore, be explained by any action on the central nervous system, nor on the cardio-inhibitory influence of the vagus either within or outside the heart.

As there are several points in the physiology of the heart that yet remain unsolved, it would be hazardous to adopt any theoretical explanation, without considerable reserve. It, however, appears probable that at least two structures are involved in the action of Strophanthus on the heart, namely, the muscular fibre itself, and a portion of the intra-cardiac nerve apparatus. The action of Strophanthus upon the muscle of the heart explains the prolonged and strengthened systolic contraction, and the ultimate standstill in extreme systole, following the administration of lethal and of toxic doses. The action upon a part of the intra-cardiac nerve apparatus explains the increased amplitude of dilatation and the prolonged diastole, which, under nice adjustments of small doses, may become permanent, and actually cause a standstill of the heart in extreme diastole. The two actions are, in a sense, antagonistic:

and when minute or therapeutic doses are given, the muscle action does not assert itself so conspicuously as the nerve action; but when the doses are large, the action on the muscle of the heart over-rides the less powerful action upon the intra-cardiac nervous structure.

Whether this latter structure can further be defined by experiment or not, the most important consideration is that the action upon it contributes greatly to enhance the value, for therapeutic purposes, of the action of Strophanthus upon the muscle of the heart; as the two actions in combination render the contractions of the heart stronger and more ample than they could be rendered by either action alone.

In thus presenting to the Society a synopsis or sketch of the observations made, during a series of years, on the Natural History, Chemistry, and Pharmacology of Strophanthus, I have endeavoured to select what appear to be the more important of the results that have been arrived at. In the pharmacological part of the observations these are probably the results that relate to the action upon the circulation. The nature of this action, determined *by pharmacological experiments*, rendered it obvious that Strophanthus would produce beneficial effects in many forms of disease of the heart. It was, therefore, employed for that purpose, and the most sanguine anticipations of its value have now been amply confirmed.